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ORIGINAL ARTICLE

Antimicrobial susceptibility and clinical outcomes of *Candida parapsilosis* bloodstream infections in a tertiary teaching hospital in Northern Taiwan

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Background: *Candida parapsilosis* is an emerging non-*albicans Candida* that is associated with central line-associated infection. *C. parapsilosis* has higher minimal inhibitory concentration to echinocandin than *Candida albicans*, and the effects of echinocandin on *C. parapsilosis* are ambiguous. Therefore, in this study, we aimed to investigate the susceptibility and the correlation between incidence and drug consumption.
Methods: This retrospective study was conducted in a tertiary teaching hospital in northern Taiwan between 2008 and 2012. The *Candida* species distribution, the correlation between the use of antifungal agents and the incidence of *C. parapsilosis* bloodstream infection, demographic information, clinical characteristics, mortality rate, and *in vitro* susceptibility of *C. parapsilosis* were analyzed.
Results: A total of 77 episodes from 77 patients were included for analysis. The overall 90-day mortality rate was 41.6%. The incidence of *C. parapsilosis* bloodstream infection showed a moderate positive correlation with the increased defined daily dose of echinocandin. The risk factors associated with mortality included malignancy or a metastatic tumor. Multivariate logistical regression analysis showed that patients with malignancy had higher odds ratios in

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terms of mortality. The rate of *C. parapsilosis* resistance to fluconazole was 3%, whereas the susceptibility rate was 95.5%.
Conclusion: Underlying comorbidity and malignancy were factors leading to death in patients with *C. parapsilosis* bloodstream infection. Catheter removal did not influence the mortality rate. The survival rate of patients receiving echinocandin was lower than the group receiving fluconazole. Fluconazole remains the drug of choice to treat *C. parapsilosis* bloodstream infections.

Introduction

Candida parapsilosis was the third most isolated pathogen among *Candida* species in both North America and Taiwan.[1,2] According to an epidemiological study in North America, *C. parapsilosis* accounted for 15.9% of all isolated organisms from 3648 patients.[2] It is higher in some hospital services, such as neonatal intensive care units, where it accounts for 30.6% of all isolated *Candida* species from neonatal intensive care unit patients in North America.[2] In the epidemiological study in Taiwan, *C. parapsilosis* remains the third most frequent *Candida* species. *Candida albicans* accounts for 50% of candidemia, whereas *C. parapsilosis* accounts for about 10% of the candidemia.[1] In addition, *C. parapsilosis* accounts for 47.8% of neonatal candidemia, based on a study that enrolled 46 neonates in Taiwan from 1994 to 1997.[3] According to a review article published in 2008, the mortality rate of *C. parapsilosis* bloodstream infections was 28.5%.[4]

C. parapsilosis is a normal human commensal, which is often isolated from hand skin. It presents an oval, round, or cylindrical shape while appearing creamy, white, shiny, and smooth or wrinkled on Sabouraud dextrose agar.[5] Intact human skin limits the pathogenicity of *C. parapsilosis*. It is notorious for its affinity for catheter or prosthetic materials, capacity for forming biofilm and ability to grow in hyperalimentation solution.[6] A study in Spain revealed that the risk factors of *C. parapsilosis* infection include vascular catheterization, previous antibiotics history, previous immunosuppressive therapy, malignancy, transplant receipt, neutropenia, and previous colonization.[7] Several articles described the outbreak of *C. parapsilosis* infections either in neonate or adult intensive care units. Molecular typing methods revealed a link between hand carriage of *C. parapsilosis* from health care workers and the pathogen of the patients. Hand hygiene thus plays an important role in the prevention of the outbreak of *C. parapsilosis* infections.[4,6,8,9] With regard to the increasing incidence of *C. parapsilosis*, its correlation with a high mortality rate and association with hand hygiene, it is important to conduct further research regarding *C. parapsilosis*.

Materials and methods

Study population

A retrospective study was conducted at a 2200-bed tertiary teaching hospital with burn care and solid organ transplantation facilities, but without bone marrow transplantation facilities in northern Taiwan. We enrolled the patients whose blood culture yielded *C. parapsilosis* during hospitalization from June 2008 to June 2012. The medical records of patients were reviewed, and data such as demographic characteristics, medical history, invasive procedures, medications, laboratory data, and outcomes were collected for analysis. We also have reviewed medical literature for comparison of *C. parapsilosis in vitro* antimicrobial susceptibility.

Inclusion criteria

C. parapsilosis bloodstream infection was defined as the presence of a positive blood culture of *C. parapsilosis* with concomitant signs and symptoms of infection.[10] *C. parapsilosis* bloodstream infection was considered to be health care-associated infections if it occurred more than 48 hours after admission.[11] If multiple episodes of *C. parapsilosis* bloodstream infection occurred in the same patient during the study period, the patient was included as a study participant using only the first episode of candidemia.[12] In the study period, a total of 77 patients whose blood culture yielding *C. parapsilosis* met the inclusion criteria.

Definition of terms

Death was considered to be attributable to *C. parapsilosis* bloodstream infection if any of the following was noted during the same hospital stay: death within 7 days after a positive blood culture for *C. parapsilosis*; absence of any cause of fatality; death in the presence of clinical evidence of persistent candidiasis (e.g., persistent fever, hypotension, or positive cultures for *C. parapsilosis* at clinically involved sites, such as peritoneal fluid, renal abscess, or endophthalmitis); autopsy evidence of disseminated candidiasis; or cause of death as *C. parapsilosis* bloodstream infection on the death certificate.[13,14]

The patient was considered a survivor of *C. parapsilosis* bloodstream infection if either of the following was noted regarding the same hospital stay: survival at discharge or improvement of *C. parapsilosis* bloodstream infection associated symptoms without recurrence within 30 days.

The incidence of candidemia was defined as the number of cases of candidemia per 1000 inpatient-days.[15] Defined daily dose is a statistical measure of drug consumption, defined by the World Health Organization. It is used to standardize the comparison of drug usage between

different drugs or between different health care environments.

Species identification and antifungal susceptibility testing

Blood samples were tested daily for microbial growth using the BACTEC FX system (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, USA). Organisms were initially identified by germ tube analysis and colony morphology on Sabouraud dextrose agar. If necessary, they were determined using a VITEK 2 yeast identification card (bioMérieux SA, Marcy-l'Etoile, France). In this study, susceptibility testing of isolates was performed using eight antifungal agents (voriconazole, posaconazole, itraconazole, fluconazole, caspofungin, micafungin, anidulafungin, and amphotericin B) with a Sensititre YeastOne Colorimetric Antifungal Panel used according to the manufacturer's instructions. Susceptibilities of *C. parapsilosis* to the above antifungal agents were read according to the interpretative breakpoints approved by the European Committee on Antimicrobial Susceptibility Testing and the Clinical Laboratory Standards Institute for susceptibility testing of *Candida* species.[16]

Statistical analysis

Univariate analyses were used to identify the risk factors associated with candidemia-related death. A Pearson's Chi square test or Fisher's exact two-tailed test was used to examine nominal data, and the unpaired Student *t* test was used for continuous data. A p value of <0.05 was considered statistically significant. The independent predictors of candidemia-associated mortality were identified by stepwise logistic regression of multivariate analysis for the significant risk factors on the univariate analyses. SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA) software was used for statistical analysis. Linear regression analysis was used to analyze the trend in annual consumption of antifungal agents and the incidence of patients with candidemia over time. Pearson's product moment correlation coefficient was used to determine the relationship between annual consumption of antifungal agents and the trend in candidemia incidence. A p value of <0.05 was considered statistically significant.

Results

In Table 1, the incidence levels of candidemia in our hospital from 2008 to 2012 are listed. The overall incidence of candidemia showed a significant increase ($p < 0.05$). The incidence of individual *Candida* species did not significantly increase by year. However, the incidence of *C. parapsilosis* showed a mild decrease although it did not reach statistical significance.

A total of 77 episodes were identified retrospectively in 77 patients with *C. parapsilosis* candidemia. The univariate analysis of risk factors of *C. parapsilosis* candidemia-associated mortality in 77 patients is summarized in Table 2. About 58% (45/77) were male, and the mean age was 50.5 $\pm$ 30.9 years. About 25% (19/77) of the patients

Table 1 The incidence and *Candida* species distribution of candidemia from 2008 to 2012

Annual inpatient days		2008 565,839	2009 595,288	2010 589,075	2011 605,233	2012 578,422	*p*
Species identification		Number of isolates (%)					
Candida albicans		66 (55.9)	58 (47.5)	71 (51.1)	77 (47.5)	79 (45.1)	0.434
	Incidence	0.12	0.10	0.12	0.13	0.14	
Candida glabrata		19 (16.1)	12 (9.8)	20 (14.4)	30 (18.5)	28 (16.0)	0.363
	Incidence	0.03	0.02	0.03	0.05	0.05	
Candida parapsilosis		13 (11.0)	14 (11.4)	10 (7.2)	22 (13.6)	18 (10.3)	0.509
	Incidence	0.02	0.02	0.01	0.04	0.03	
Candida tropicalis		14 (11.8)	23 (18.9)	27 (19.4)	19 (11.7)	28 (16.0)	0.226
	Incidence	0.02	0.04	0.05	0.03	0.05	
Candida krusei		0	3 (2.5)	1 (0.7)	0	3 (1.7)	0.136
	Incidence	0	0.01	0.00	0	0.01	
Candida dubliniensis		1 (0.8)	0	1 (0.7)	0	1 (0.5)	0.775
Candida famata		0	0	0	2 (1.2)	0	0.144
Candida guilliermondii		1 (0.8)	0	1 (0.7)	5 (3.1)	3 (1.7)	0.261
Candida haemulonii		0	0	0 (0)	2 (1.2)	0	0.144
Candida lusitaniae		1 (0.8)	0	1 (0.7)	1 (0.6)	0	0.683
Candida pelliculosa		0	0	1 (0.7)	1 (0.6)	0	0.794
Candida rugosa		0	1 (0.8)	0	0	1 (0.5)	0.706
Candida utilis		0	1 (0.8)	0	0	0	0.335
Candida lipolytica		0	0	1(0.7)	0	0	0.529
Candida norvegensis		0	0	0	0	1 (0.5)	$p > 0.999$
Candida species		3 (2.5)	10 (8.2)	5 (3.6)	3 (1.9)	13 (7.4)	0.031
Total		118	122	139	162	175	0.002

Table 2 Univariate analysis of risk factors of *Candida parapsilosis* candidemia-associated mortality

Variable (%)	Survival (n = 45)	Death (n = 32)	p
Sex, male	25 (55.6)	20 (62.5)	0.542
Age < 8 y	16 (35.6)	3 (9.4)	0.009
Onset of candidemia in ICU	16 (35.6)	3 (9.4)	0.009
Underlying disease			
Recent intra-abdominal surgery	13 (28.9)	9 (28.1)	0.942
Recent chemotherapy	8 (17.8)	12 (37.5)	0.052
Chronic steroid therapy	3 (6.7)	3 (9.4)	0.688
Diabetes mellitus	8 (17.8)	12 (37.5)	0.913
End-stage renal disease	3 (6.7)	1 (3.1)	0.637
COPD	1 (2.2)	4 (12.5)	0.154
Chronic liver disease	7 (15.6)	7 (21.9)	0.479
Any maligency	17 (37.8)	26 (81.3)	<0.001
Leukemia	1 (2.2)	2 (6.3)	0.567
Gastrointestinal malignancy	8 (17.8)	10 (31.3)	0.169
Metastatic solid tumor	5 (11.1)	11 (34.4)	0.013
Neutropenia	6 (13.3)	5 (15.6)	>0.999
Catheter			
Hickmann catheter	4 (8.9)	1 (3.1)	0.395
Port-A	12 (26.7)	14 (50)	0.118
CVC	28 (62.2)	16 (50)	0.285
Femoral CVC	12 (26.7)	6 (18.8)	0.419
Catheter all	44 (91.1)	31 (93.8)	>0.999
Remove CVC	26 (33.8)	26 (33.8)	0.410
TPN	4 (8.9)	2 (6.3)	>0.999
PPN	13 (28.9)	15 (46.9)	0.106
TPN + PPN	17 (37.8)	17 (53.1)	0.181
Fluconazole	26 (59.1)	18 (40.9)	0.894
Echinocandin	6 (46.2)	7 (53.8)	0.324
Amphotericin B	9 (81.8)	2 (18.2)	0.089
Voriconazole	3 (50)	3 (50)	0.894

COPD = chronic obstructive pulmonary disease; CVC = central venous catheter; ICU = intensive care unit; PPN = partial parenteral nutrition; TPN = total parenteral nutrition.

were younger than 18 years. The overall mortality attributable to *C. parapsilosis* candidemia was about 42% (32/77). Risk factors of mortality in the univariate analysis included patients with malignancy ($p < 0.001$) or a metastatic tumor ($p = 0.013$). By contrast, patients younger than 18 years and or whose candidemia was discovered in the intensive care unit showed a better survival rate ($p = 0.009$). A multivariate logistic regression analysis, the results of which are listed in Table 3, showed that patients with malignancy had a higher odds ratio in terms of mortality ($p = 0.045$).

A total of 75 patients (75/77) had a central line-associated route when they acquired a *C. parapsilosis* bloodstream infection. Five patients had a Hickman catheter, 26 patients had a port-A, and 44 patients had a central venous catheter (CVC), which included 18 patients with femoral CVC. However, the kind of catheter used did not contribute to mortality (Table 2).

The minimal inhibitory concentration (MIC) of 67 *C. parapsilosis* in our study, which were identified by YeastOne commercial disk, is summarized in Table 4. The MIC_{50}/MIC_{90} of fluconazole was 1/2 (range 0.25–8), amphotericin B was 1/1 (range 0.25–1), anidulafungin was 1/2 (range 0.12–2), micafungin was 1/2 (range 0.25–4), caspofungin was 0.5/1 (range 0.25–1), voriconazole was 0.008/0.15 (range 0.008–0.15), posaconazole was 0.03/0.06 (range 0.015–0.12), and itraconazole was 0.06/0.12 (range 0.015–0.25). The *C. parapsilosis* susceptibility rate to fluconazole was 95.5%, whereas the resistance rate was 3%. We included papers mentioning the fluconazole resistance rate of *C. parapsilosis* and those giving full coverage of antifungal agents. The result is also listed in Table 4.

The correlation between the annual consumption of antifungal agents and the incidence of *C. parapsilosis* bloodstream infection was calculated using Pearson's product moment correlation coefficient (results shown in Table 5). The incidence of *C. parapsilosis* bloodstream infection increased, whereas the annual consumption of echinocandin increased during the study period. *C. parapsilosis* bloodstream infection showed a moderate positive correlation with the use of echinocandin, but this correlation was not statistically significant (Pearson correlation = 0.614, $p = 0.271$).

Discussion

The incidence of all candidemia cases in the hospital was 0.25 per 1000 patient-days, which shows a significant increase from 2008 to 2012; the incidence also increased significantly from 0.10 to 0.15 per 1000 patient-days from 1999 to 2006 in Taiwan.[1] In the meantime, the incidence of candidemia ranged from 0.45 to 0.46 per 1000 admission-days in America and ranged from 0.2 to 0.38 in Europe.[17] Ruan and Hsueh[17] mentioned that the incidence of candidemia from 1980 to the end of 1990s increased. This was followed by a relatively stable period in Taiwan, but it continued to increase significantly in the 2000s.[17]

The distribution of *Candida* species shows regional differences.[18] In this study, C. *albicans* (49.0%) was the most frequently isolated species, followed by *C. tropicalis* (15.5%), *C. glabrata* (15.2%), and *C. parapsilosis* (10.8%). The rate of isolated *C. parapsilosis* was 13.3%, which is close to the average rate in the Asia-Pacific area (13.7%), but lower than the global average (17.2%) from 2008 to 2009.[19] Three studies during 1994 to 2000 from northern Taiwan reported the rate of isolated *C. parapsilosis* to be around 11.2–17.5%.[20–22] Pfaller et al[23,24] reported global data showing that the rate of isolated *C. parapsilosis* from 1992 to 2001 was 13.1% and 15%. The distribution in the

Table 3 Multivariate logistic regression analysis of risk factors associated with mortality in episodes of candidemia

	Odds ratio	95% CI	p
Age < 18 y	0.39	0.09–1.79	0.227
Onset of candidemia in ICU	0.77	0.13–4.39	0.767
Any malignancy	4.08	1.03–16.14	0.045
Metastatic solid tumor	1.72	0.46–6.45	0.419

CI = confidence interval; ICU = intensive care unit.

Table 4 *In vitro* activities of antifungal agents against *Candida parapsilosis*

Author	Time	Location	MIC_{50}/MIC_{90}							Fluconazole
			Fluconazole	Caspofungin	Micafungin	Anidulafungin	Amphotericin B	Voriconazole	Posaconazole	Itraconazole	Susceptible/resistant%
Lin	2008—2012	Taiwan	1/2	0.5/1	1/2	1/2	1/1	0.008/0.15	0.03/0.06	0.06/0.12	95.5/3
Hsueh	1981—2000	Taiwan					0.5/1	0.12/0.12		0.12/0.25	98/0
Yang	1999—2002	Taiwan									100/0
Hsueh	2003	Taiwan									100/0
Ruan	2005—2007	Taiwan		1/2	2/2	1/2	1/1	0.03/0.06	0.03/0.06	0.06/0.25	98/0
Wei Liu	2009—2011	China	4/8	0.25/0.25			0.5/0.5	0.03/0.125		0.5/1	40/16
Fang Li	2006—2011	China	1/1	1/1.5			0.5/0.5	0.064/0.064		0.125/0.125	*/0
Ostrosky-Zeichner	1995—1999	America		2/2	1/2	2/2	0.13/0.5	0.03/0.06	0.03/0.13		
Cuenca-Estrella	2001—2006	Europe		0.5/1			0.12/0.25	0.02/0.03	0.02/0.03		
Pfaller	2001—2004	Global		0.5/1	1/2	2/4				0.25/0.5	*/3.2
Eike	2008	Global		*/0.5—4				*/0.03—0.25	*/0.03—0.25		

Table 5 Correlation between the use of the antifungal agents and the incidence of *Candida parapsilosis* bloodstream infection

		C. parapsilosis
Fluconazole total	Pearson correlation	−0.643
	Sig. (2-tailed)	0.241
Fluconazole IV	Pearson correlation	−0.486
	Sig. (2-tailed)	0.407
Fluconazole oral	Pearson correlation	−0.586
	Sig. (2-tailed)	0.299
Echinocandin total	Pearson correlation	0.614
	Sig. (2-tailed)	0.271
Caspofungin	Pearson correlation	−0.086
	Sig. (2-tailed)	0.891
Micafungin	Pearson correlation	0.800
	Sig. (2-tailed)	0.104
Anidulafungin	Pearson correlation	0.390
	Sig. (2-tailed)	0.516
Voriconazole	Pearson correlation	−0.162
	Sig. (2-tailed)	0.795
Amphotericin B	Pearson correlation	−0.787
	Sig. (2-tailed)	0.114

hospital was similar to that reported in the Asia-Pacific area, and although *C. tropicalis* was higher than *C. glabrata*, the rates of the following three non-*albicans Candida* spp. were close.

C. parapsilosis is a common skin colonizer. It is most often isolated from neonates and children and related to intravenous instrumentation. The risk factors of patients who developed *C. parapsilosis* bloodstream infections include prolonged use of catheter or indwelling device, hyperalimentation solution infusion, gastrointestinal surgery, presence of immune compromising conditions such as AIDS, recent chemotherapy or use of immune compressive agents, previous colonization, previous antibiotics treatment, or previous antifungal agent treatment.[4] Chen et al[25] found that patients with *C. parapsilosis* bloodstream infections had higher blood albumin levels, lower Sequential Organ Failure Assessment scores, and frequently those who had total parental nutrition infusions would have lower mortality rates. In our study, the mortality rate was 41.6%, which is higher than that (28.5%) reported in a review article in 2008 or in 2012 (30%).[2,4] The risk factors of mortality included those patients with any malignancy or presence of a metastatic tumor. By contrast, patients younger than 18 years had lower mortality rates. Furthermore, in multivariate logistical regression analysis, patients with malignancy had a higher odds ratio in terms of mortality. However, the drug selection, total parental nutrition infusion, type of catheter, or the site of CVC did not increase the risk of mortality. Andes et al[26] report that echinocandin, CVC removal, and Acute Physiology and Chronic Health Evaluation II score were independently associated with mortality in non-*albicans Candida* species infections, but only disease severity predicted the survival of patients with *C. parapsilosis* and *C. tropicalis* infections. In our study, the results supported similar conclusions—that underlying comorbidity and malignancy

were the factors leading to death. *C. parapsilosis* bloodstream infection was merely a confounding accident.

The Infectious Diseases Society of America guidelines for the management of candidiasis in 2009 suggested fluconazole for nonneutropenic patients with *C. parapsilosis* infections, and fluconazole or liposomal amphotericin B for neutropenic patients. The susceptibility of *C. parapsilosis* to echinocandin was susceptible to resistance, even though *in vitro* resistance was uncommon.[27] The *in vitro* activity of antifungal agents against *C. parapsilosis* from this study and other articles are summarized in Table 4.[28–37] About 3% of isolated *C. parapsilosis* in our study were resistant to fluconazole. This rate is similar to the global data. However, a high resistance rate of fluconazole was noted in China. The authors of two articles mentioned the cross resistance between fluconazole and voriconazole, and suggested using non-azole antifungal agents and consistently monitoring susceptibility.[32,33] Echinocandin is a new class of antifungal agents. The echinocandin MICs of *C. parapsilosis* are higher than those of other *Candida* species. In our study, only one isolated *C. parapsilosis* was intermediate to micafungin. The other isolates were susceptible to *in vitro* echinocandin. However, the survival rate of patients receiving echinocandin was lower than that of patients receiving fluconazole (46.2% vs. 59.1%). Amphotericin B was traditionally the most commonly prescribed antifungal agent. The reported resistance rate of *C. parapsilosis* to amphotericin B was 2–3%.[4] In our study, no isolated *C. parapsilosis* was resistant to amphotericin B *in vitro*. The clinical response was better compared with other agents. However, because of its nephrotoxicity and the high cost of liposomal amphotericin B, their annual consumption was on the decrease. In our study, fluconazole remains the drug of choice to treat *C. parapsilosis* bloodstream infections.

Caspofungin was introduced to our hospital in 2003, followed by micafungin in 2009, and then anidulafungin in 2011. It is hypothesized that the increasing use of antifungal agents, such as fluconazole, increases the selection pressure on non-*albicans Candida* species. However, conflicting results have been reported, and thus the hypothesis remains controversial.[17] Given the high MIC of *C. parapsilosis*, some articles mention the selection pressure associated with the increasing use of echinocandin.[2] However, Lai et al[15] reported a significant negative correlation between the incidence of *C. parapsilosis* infection and the use of echinocandin and voriconazole. In our study, *C. parapsilosis* bloodstream infection showed a moderate positive correlation with the use of echinocandin, but this correlation was not statistically significant. Many factors influence the incidence of *C. parapsilosis* bloodstream infection. The advocacy of hand hygiene campaign started in our hospital in 2009. Furthermore, the CVC care bundle was launched in the intensive care unit in our hospital in 2010. The reinforcement of infection control would reduce the infection rate of *C. parapsilosis*. Although the use of antifungal agents is not the only factor influencing the incidence of *C. parapsilosis* infection, our study does not support the hypothesis that increasing use of echinocandin increases the incidence of *C. parapsilosis* infection.

Underlying comorbidity and malignancy were factors leading to death in patients with *C. parapsilosis* bloodstream infection. Catheter removal did not influence the mortality rate. The survival rate of patients receiving echinocandin was lower than that in the group receiving fluconazole. Fluconazole remains the drug of choice to treat *C. parapsilosis* bloodstream infections.

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